EXHIBIT 602.13

℞ TREATMENT

Initial management involves general supportive measures and gastrointestinal decontamination. Antidotal therapy using amyl nitrite, sodium nitrite, and sodium thiosulfate (the Lilly cyanide antidote kit) coupled with high-dose oxygen should be administered as soon as possible to patients with altered mental status, abnormal vital signs, or metabolic acidosis. The rationale for antidotal therapy is as follows. Nitrites induce methemoglobinemia. Methemoglobin has a higher affinity for cyanide than does cytochrome oxidase and thus promotes its dissociation from this enzyme. Thiosulfate reacts with the cyanide as the latter is slowly released from cyanomethemoglobin, forming the relatively nontoxic thiocyanate, which is excreted in the urine. Oxygen reverses the binding of cyanide to cytochrome oxidase sites and enhances the efficacy of sodium nitrite and sodium thiosulfate, in addition to acting as a substrate for metabolism.

Amyl nitrite is administered for 30 s of each minute. The ampule is broken between two pads of gauze and placed over the airway while the patient breathes spontaneously or is ventilated by a bag-mask unit. A new ampule should be used every 3 min. This process is continued while sodium nitrite is being prepared, but it may be omitted if endotracheal intubation has been performed. Sodium nitrite is administered intravenously as a 3% solution at a rate of 2.5 to 5.0 mL/min up to a total dose of 10 to 15 mL (300 to 450 mg). Sodium thiosulfate is then administered intravenously as a 25% solution at a dose of 50 mL (12.5 g) given over 1 to 2 min. With recurrent or persistent symptoms, half or full doses of both sodium nitrite and sodium thiosulfate are administered. Hyperbaric oxygen therapy should be considered in patients who fail to respond to antidotal therapy.

DIGOXIN Poisoning with digitalis (cardiac glycoside) occurs most often during therapeutic or suicidal use of digoxin and on occasion with plant (oleander) ingestion. Cardiac glycosides act by inhibiting the enzyme sodium-potassium ATPase, leading to increased intracellular levels of Na^+ and Ca^{2+} and decreased intracellular K^+ levels. Digoxin is slowly absorbed and slowly distributed. Serum levels may not correlate with pharmacologic effects for up to 8 h following a therapeutic oral dose. Digoxin is 25 to 30 percent protein-bound in the plasma, has a large volume of distribution of 5 to 6 L/kg body weight, and is localized in skeletal muscle, liver, and heart. Elimination is primarily by renal excretion. The half-life ranges between 36 and 45 h, is prolonged in hepatic failure and in renal failure, and may be shortened in overdose. Approximately 60 percent of a dose is excreted unchanged by the kidneys, and the remainder is metabolized by the liver to inactive metabolites. Therapeutic serum concentrations range from 0.6 to 2.5 nmol/L (0.5 to 2.0 ng/mL).

Clinical Toxicity Symptoms of toxicity include vomiting, confusion, delirium, and occasionally hallucinations, blurred vision, photophobia, scotomata, and disturbed color perception. Cardiac manifestations include sinus arrhythmia, sinus bradycardia, and all degrees of atrioventricular block. Premature ventricular contractions, bigeminy, ventricular tachycardia, and fibrillation also occur. The combination of supraventricular tachyarrhythmia and AV block is highly suggestive of digitalis toxicity. While bradyarrhythmias and hypokalemia are common with chronic intoxication, tachyarrhythmias and hyperkalemia are generally seen with acute poisoning. Similarly, serum digoxin levels may be minimally elevated or even therapeutic in chronic toxicity, whereas they are usually markedly elevated following acute overdose. Clinical toxicity occurs with digoxin levels in excess of 3.8 to 6.4 nmol/L (3 to 5 ng/mL), and levels as high as 64 to 77 nmol/L (50 to 60 ng/mL) have been seen following acute overdose.

Diagnosis The diagnosis is confirmed by finding an elevated serum digoxin level. Since toxicology screening tests do not detect cardiac glycosides, a quantitative drug level must be ordered specifically.

℞ TREATMENT

Gastrointestinal decontamination should be accomplished as soon as possible. Since emesis and gastric intubation may cause vagal stimulation and worsen existing conduction block, activated charcoal is preferred. Repeated doses should be administered because this therapy also can enhance elimination of digoxin. Diuresis, hemodialysis, and hemoperfusion are ineffective, however. Potassium, magnesium, and calcium abnormalities should be corrected. Electrical pacing may be necessary when sinus bradycardia and second- and third-degree heart block result in hypotension and fail to respond to atropine, isoproterenol, or antibody therapy. Magnesium sulfate (as for antiarrhythmic poisoning), phenytoin, and lidocaine may be useful in the treatment of ventricular tachyarrhythmias. Digoxin-specific Fab-fragment antibodies should be administered to patients with potentially life-threatening toxicity not immediately responsive to the above. Following antibody administration, cardiac arrhythmias and hyperkalemia are generally corrected within an hour; the antibodies are given intravenously over 30 min, unless cardiac arrest has occurred, in which case the solution is given as a bolus. The drug-antibody complex is excreted in the urine with a half-life of 16 to 20 h. In patients with renal failure, the drug-antibody complex is metabolized over a period of days to weeks. Although free digoxin levels decrease rapidly to zero following antibody administration, routine methods used to measure digoxin do not differentiate between bound and unbound drug, so that drug levels do not correlate with toxicity after antibody therapy. Antibodies cross-react with other cardiac glycosides, but larger doses may be needed for toxicity not involving digoxin.

Each 40 mg vial of antibody can neutralize 0.6 mg of digoxin. Formulas and tables for calculating the dose of antibody based on body weight and post-distribution serum digoxin level or the amount of drug acutely ingested are available in the package insert. Unfortunately, toxicity may occur before distribution is complete or before levels are available. In addition, the amount of an acute overdose may be unknown, and calculated doses often exceed the effective dose (leading to costly overtreatment). The following doses are therefore suggested. With chronic digoxin intoxication, when total-body drug load only slightly exceeds the therapeutic amount and when patients may be dependent on digoxin for its inotropic effects, an antibody dose of 1 to 2 vials is usually sufficient. In acute poisoning drug levels are generally higher, and 5 to 10 vials are usually required. These doses can be repeated as necessary.

ETHYLENE GLYCOL Ethylene glycol is a colorless, odorless, sweet-tasting, water-soluble liquid that is used as a solvent for paints, plastics, and pharmaceuticals and in the manufacture of explosives, fire extinguishers, foams, hydraulic fluids, windshield cleaners, radiator antifreeze, and de-icer preparations.

Ethylene glycol is absorbed rapidly, and levels peak approximately 2 h after ingestion. Ethylene glycol has a volume of distribution of 0.6 to 0.8 L/kg body weight. It is oxidized by alcohol dehydrogenase to glycoaldehyde, which is metabolized successively to glycolic acid, glyoxylic acid, and oxalic acid. As much as 20 percent is excreted unchanged in the urine. The half-life ranges from 3 to 8 h. Since alcohol dehydrogenase has a higher affinity for ethanol than for ethylene glycol, ethanol is metabolized preferentially when both alcohols are present, and the half-life of ethylene glycol is then prolonged to about 17 h.

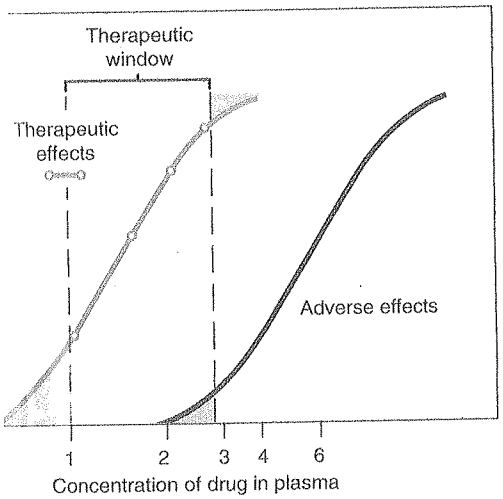
Ethylene glycol and its metabolites produce CNS depression. Ethylene glycol is more potent than ethanol in this respect. The glycolic acid metabolite is even more toxic than ethylene glycol. It causes a metabolic acidosis with an increased anion gap and interstitial and tubular damage to the kidney. Glyoxylic acid is more toxic still, but it is metabolized rapidly to oxalic acid and contributes little to the organ toxicity. Oxalic acid may precipitate as calcium oxalate crystals in the brain, heart, kidney, lung, pancreas, and urine and cause hypocalcemia.

ribution, and other factors combine to yield a evels in patients given the same dose. Further- oncompliance with prescribed regimens during an endemic and elusive cause of therapeutic inical indicators assist in the titration of some l range, and no chemical determination is a bservations of the response to treatment. How- ıd adverse effects are not precisely quantifiable complex clinical situations, estimates of the e misleading. For example, previously existing / obscure the neurologic consequences of intoxi- Because clearance, half-life, accumulation, and vels are difficult to predict, the measurement of useful as a guide to the optimal dose. This is ı there is a narrow range between the plasma utic and adverse effects. For drugs having such digoxin, theophylline, lidocaine, aminoglyco- ants—dose optimization should involve modifi- dose on the basis of the pharmacokinetic princi- In certain instances, predictive nomograms and developed to facilitate the necessary modifica- ost flexible and accurate method for individualiz- ears to be a feedback approach using a small obtained plasma levels and Bayesian forecasting. this type of computer-assisted dosing has been ient care. However, the overall cost/benefit ratio routine management still remains to be concu-

ı narrow therapeutic window that exhibit first- en, dosage adjustments may be made on the as- rage, maximum, and minimum steady state con- ed linearly to the dosing rate. Accordingly, the d on the basis of the ratio between the desired ntrations:

$$\frac{C_{ss}\text{ (desired)}}{C_{ss}\text{ (measured)}} = \frac{\text{dose (new)}}{\text{dose (previous)}}$$

dose-dependent kinetics (e.g., phenytoin and the- oncentrations change disproportionately more than dosing rate. Not only should changes in dose be e degree of unpredictability, but plasma concentra- ı is critical to ensure appropriate modification. mong individual responses to given plasma levels . This is illustrated by a hypothetical population nse curve (Fig. 68-6) and its relationship to the



cumulative percentage of patients responding to increas- plasma with both therapeutic and adverse effects. The efines the range of concentrations of drug that will achieve most patients with adverse effects in only a small per-

Table 68-5

Concentrations of Drugs in Plasma: Relation to Efficacy and Adverse Effects

Drug	Efficacy*	Adverse Effects†
Amikacin (peak)	20 μg/mL	40 μg/mL
Carbenicillin	100 μg/mL‡	300 μg/mL
Carbamazepine	3 μg/mL	10 μg/mL
Digitoxin	12 ng/mL	25–30 ng/mL
Digoxin	0.8 ng/mL	2.0 ng/mL
Ethosuximide	40 μg/mL	100 μg/mL
Gentamicin (peak)	5 μg/mL	10 μg/mL
Gentamicin (predose)		2.0 μg/mL
Lidocaine	1.5 μg/mL	5 μg/mL
Lithium	0.5 mEq/L	1.3 mEq/L
Penicillin G	1–25 μg/mL§	
Phenytoin (diphenylhydantoin)	10 μg/mL	20 μg/mL
Procainamide	4 μg/mL	10 μg/mL
Quinidine	2.5 μg/mL	6 μg/mL
Theophylline	8 μg/mL	20 μg/mL

* The therapeutic effect is infrequent or slight at levels below these.
† The frequency of adverse effects increases sharply when these levels are exceeded.
‡ Minimal inhibitory concentration (MIC) for most strains of *Pseudomonas aeruginosa*. MIC for other, more sensitive, organisms is less.
§ There is a wide range of MIC of penicillin for various organisms, and the MIC of all those for which penicillin is used is <20. "Massive" penicillin therapy with 20 million units daily achieves levels of 20 to 25 μg/mL in patients with clearance of creatinine of 100 mL/min.

therapeutic range or therapeutic window of desired plasma levels. The defined therapeutic window should include the levels at which the intended pharmacologic effect is achieved in most patients. However, a few persons, who are sensitive to the therapeutic effects, respond to lower levels, whereas others are refractory enough to require levels that may cause adverse effects. For example, a few patients with strong seizure foci require plasma levels of phenytoin exceeding 20 μg/mL to control seizures. Dosages to achieve this effect may be appropriate.

As also illustrated in Fig. 68-6, some patients are prone to adverse effects at levels that are tolerated by most of the population. Therefore, raising the plasma concentration of a drug to a level that has a high probability of being therapeutically effective may bring on unwanted actions in an occasional patient. Table 68-5 presents for a number of drugs the plasma concentrations that are associated with adverse and therapeutic effects in most patients. Use of this information according to the guidelines discussed should permit more effective and safer therapy for those patients who are not "average."

EFFECTIVE PARTICIPATION OF THE PATIENT IN THERAPY Measurement of the concentration of a drug in plasma is the most effective way to detect failure to take a drug. Such "noncompliance" is a frequent problem in the long-term treatment of diseases such as hypertension and epilepsy, occurring in 25 percent or more of patients in therapeutic environments in which no special effort is made to involve patients in the responsibility for their own health. Occasionally, noncompliance can be uncovered by sympathetic, nonincriminating questioning, but more often it is recognized only after determining that the concentration of drug in plasma is nil or is recurrently low. Because other factors can cause plasma levels to be lower than expected, comparison with levels obtained during inpatient treatment may be required to confirm that noncompliance has occurred. Once the physician is certain of noncompliance, a nonaccusatory discussion of the problem with the patient may clarify the reason for the noncompliance and serve as a basis for more effective cooperation on the part of the patient. Many approaches have been tried to make patients exercise more responsibility for their own treatment, most based on better communication regarding the nature of the disease and the chances of success or failure of the treatment. The patient is given a chance to discuss problems associated with treatment. The process may be improved by the involvement of nurses and other

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EDITORS

Anthony S. Fauci, MD
Chief, Laboratory of Immunoregulation; Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda

Eugene Braunwald, AB, MD, MA (Hon), MD (Hon), ScD (Hon)
Distinguished Hersey Professor of Medicine, Faculty Dean for Academic Programs at Brigham and Women's Hospital and Massachusetts General Hospital, Harvard Medical School; Vice-President for Academic Programs, Partners HealthCare System, Boston

Kurt J. Isselbacher, AB, MD
Mallinckrodt Professor of Medicine, Harvard Medical School; Physician and Director, Massachusetts General Hospital Cancer Center, Boston

Jean D. Wilson, MD
Charles Cameron Sprague Distinguished Chair and Clinical Professor of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas

Joseph B. Martin, MD, PhD, FRCP (C), MA (Hon)
Dean of the Faculty of Medicine; Caroline Shields Walker Professor of Neurobiology and Clinical Neuroscience, Harvard Medical School, Boston

Dennis L. Kasper, MD, MA (Hon)
William Ellery Channing Professor of Medicine, Harvard Medical School; Director, Channing Laboratory; Co-Director, Division of Infectious Diseases; Executive Vice-Chairman, Department of Medicine, Brigham and Women's Hospital, Boston

Stephen L. Hauser, MD
Chairman and Betty Anker Fife Professor, Department of Neurology, University of California San Francisco, San Francisco

Dan L. Longo, AB, MD, FACP
Scientific Director, National Institute on Aging, National Institutes of Health, Gerontology Research Center, Bethesda and Baltimore

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